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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,508	QU ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *2/3/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *17-18, 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 19-27, 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 1, claims 1-16, 19-27 and 29-39 in the reply filed on February 3, 2006 is acknowledged.

2. Claims 17-18 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 3, 2006.

3. Claims 1-16, 19-27 and 29-39 are pending and will be examined.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on May 7, 2004 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claims 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. As currently written, claim 12 recites the same claim language and depends from the same independent claim as claim 2.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 recites the limitation "the live tissue sample" in the body of the claim. The claim recites a method which depends from claim 1 which makes no mention of a live tissue sample. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 3-10, 13, 34 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

With regard to claim 1, Lindpainter teaches a method of determining an angiotensin converting enzyme genotype in a sample comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 707, 'determination of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples); and b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the ACE genotype in the sample (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved).

With regard to claim 3, Lindpainter teaches an embodiment of caim 1, wherein the sample is a human sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 4, Lindpainter teaches an embodiment of claim 3, wherein the method distinguishes between genotypes selected from the goup consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 1, where II, ID and DD genotypes are disclosed).

With regard to claim 5, Lindpainter teaches an embodiment of claim 3, wherein the DNA is undegraded DNA (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to 6, Lindpainter teaches an embodiment of claim 5, wherein the sample is a live tissue sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 7, Lindpainter teaches an embodiment of claim 6, wherein the sample is selected from the group consisting of: blood (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 8, Lindpainter teaches an embodiment of claim 1, wherein the live tissue sample is blood (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 9, Lindpainter teaches an embodiment of claim 3, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 10, Lindpainter teaches an embodiment of claim 3, wherein the ACE sequence is a 287 bp nonsense DNA domain (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 13, Lindpainter teaches an embodiment of claim 3, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were

identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 34, Lindpainter teaches a method of determining a genotype for a gene of interest in a sample, comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking a gene sequence, the presence of which indicates the presence of a first gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said gene sequence and together with one of the flanking primers forms a second pair of primers (p. 707, 'determination of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples); and

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the genotype of the gene of interest in the sample (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved);

With regard to claim 36, Lindpainter teaches an embodiment of claim 34, wherein the sample is a human sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 37, Lindpainter teaches an embodiment of claim 34, wherein the DNA sample is from a source selected from the group consisting of a biological fluid (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were

identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

7. Claims 1, 3-10, 13, 34 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Teranishi et al. (Journal of Hypertension, 1999, vol. 17, p. 351-356). Teranishi discloses an investigation of the association between the insertion/deletion polymorphism in the angiotensin converting enzyme and the microvascular structure of patients with non-Diabetic renal disease (Abstract).

With regard to claim 1, Teranishi teaches a method of determining an angiotensin converting enzyme genotype in a sample comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele); and

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the ACE genotype in the sample (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the

deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele).

With regard to claim 3, Teranishi teaches an embodiment of caim 1, wherein the sample is a human sample (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 4, Teranishi teaches an embodiment of claim 3, wherein the method distinguishes between genotypes selected from the goup consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Table 1, where II, ID and DD genotypes are disclosed in classifying patients).

With regard to claim 5, Teranishi teaches an embodiment of claim 3, wherein the DNA is undegraded DNA (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to 6, Teranishi teaches an embodiment of claim 5, wherein the sample is a live tissue sample (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 7, Teranishi teaches an embodiment of claim 6, wherein the sample is selected from the group consisting of: blood (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 8, Teranishi teaches an embodiment of claim 1, wherein the live tissue sample is blood (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 9, Teranishi teaches an embodiment of claim 3, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 351, col. 1, where the details of the ACE gene sequence and the polymorphism are disclosed).

With regard to claim 10, Teranishi teaches an embodiment of claim 3, wherein the ACE sequence is a 287 bp nonsense DNA domain (p. 351, col. 1, where the details of the ACE gene sequence and the polymorphism are disclosed).

With regard to claim 13, Teranishi teaches an embodiment of claim 3, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 34, Teranishi teaches a method of determining a genotype for a gene of interest in a sample, comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking a gene sequence, the presence of which indicates the presence of a first gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said gene sequence and together with one of the flanking primers forms a second pair of primers (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele); and

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the genotype of the gene of interest in the sample (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele);

With regard to claim 36, Teranishi teaches an embodiment of claim 34, wherein the sample is a human sample (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 37, Teranishi teaches an embodiment of claim 34, wherein the DNA sample is from a source selected from the group consisting of a biological fluid (p. 352, col. 1,

'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

8. Claims 1-10, 12-13 and 34-37 rejected under 35 U.S.C. 102(a) as being anticipated by Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666). Lin teaches a real-time PCR amplification for rapid genotyping of the angiotensin-converting enzyme insertion/deletion polymorphism (Abstract).

With regard to claim 1, Lin teaches a method of determining an angiotensin converting enzyme genotype in a sample comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 662, col. 1, 'genotyping of ACE gene I/D allele by conventional PCR' and col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction); and

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the ACE genotype in the sample (Figures 2-3, where II, DD, and ID polymorphic profiles are shown; see also col. 1-2, conventional PCR, where the PCR products were separated on 2% agarose gels, yielding a 490, 190 and undisclosed 3rd amplicon size).

With regard to claim 2 and 12, Lin teaches an embodiment of claim 1, wherein the amplification comprises performing a single polymerase chain reaction amplification (p. 662, col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction).

With regard to claim 3, Lin teaches an embodiment of caim 1, wherein the sample is a human sample (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 4, Lin teaches an embodiment of claim 3, wherein the method distinguishes between genotypes selected from the goup consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 2A, where II, DD, and ID melting curves are distinguished).

With regard to claim 5, Lin teaches an embodiment of claim 3, wherein the DNA is undegraded DNA (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to 6, Lin teaches an embodiment of claim 5, wherein the sample is a live tissue sample (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood

samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 7, Lin teaches an embodiment of claim 6, wherein the sample is selected from the group consisting of: blood (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 8, Lin teaches an embodiment of claim 1, wherein the live tissue sample is blood (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 9, Lin teaches an embodiment of claim 3, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 661, col. 1).

With regard to claim 10, Lin teaches an embodiment of claim 3, wherein the ACE sequence is a 287 bp nonsense DNA domain (p. 661, col. 1).

With regard to claim 13, Lin teaches an embodiment of claim 3, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 34, Lin teaches a method of determining a genotype for a gene of interest in a sample, comprising:

a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking a gene sequence, the presence of which indicates the presence of a first gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said gene sequence and together with one of the flanking primers forms a second pair of primers (p. 662, col. 1, 'genotyping of ACE gene I/D allele by conventional PCR' and col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction); and

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the genotype of the gene of interest in the sample (Figures 2-3, where II, DD, and ID polymorphic profiles are shown; see also col. 1-2, conventional PCR, where the PCR products were separated on 2% agarose gels, yielding a 490, 190 and undisclosed 3rd amplicon size);

With regard to claim 35, Lin teaches an embodiment of claim 34, wherein the amplification comprises performing a single polymerase chain reaction amplification (p. 662, col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction).

With regard to claim 36, Lin teaches an embodiment of claim 34, wherein the sample is a human sample (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood

samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

With regard to claim 37, Lin teaches an embodiment of claim 34, wherein the DNA sample is from a source selected from the group consisting of a biological fluid (Abstract, 'design and method' heading, where the samples were forth human genomic DNA samples; p. 662, col. 1, 'isolation of genomic DNA' heading, where blood samples were obtained from a sample bank at the Department of Internal Medicine at the National Taiwan University).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 11, 14-16, 19, 21-26 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) as applies to claims 1, 3-10, 13, 34 and 36-37 and further in view of Soubrier et al. (US Patent 5,736,323; April 1998) and further in view of Buck et al. (Biotechniques (1999) 27(3):528-536). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 1, 3-10, 13, 34 and 36-37 as recited in the 102 rejection stated above.

With regard to claim 14-15, Lindpainter teaches an embodiment of claims 3 or 11, wherein the nucleic acid products consist of a first nucleic acid fragment of approximately 123 base pairs, a second nucleic acid fragment of approximately 157 base pairs, and a third nucleic acid fragment of approximately 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

With regard to claim 16, Lindpainter teaches an embodiment of claim 15, wherein:
a) when the first nucleic acid fragment is not present and the second and third nucleic acid fragments are present, the genotype is I/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype); and
b) when the first nucleic acid fragment is present and the second and the third nucleic acid fragments are not present, the genotype is D/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype).

With regard to claim 19, Lindpainter teaches a method for determining an angiotensin converting enzyme (ACE) genotype in a sample, comprising:
a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and

together with one of the flanking primers forms a second pair of primers (p. 707, 'determination of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples); and b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the ACE genotype in the sample (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved);

With regard to claim 21, Lindpainter teaches an embodiment of claim 19, wherein the sample is a human sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 22, Lindpainter teaches an embodiment of claim 21, wherein the method distinguishes between genotypes, selected from the group consisting of: insertion/insertion, insertion/deltion, deletion/deletion (Figure 1, where II, ID and DD genotypes are disclosed).

With regard to claim 23, Lindpainter teaches an embodiment of claim 21, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 24, Lindpainter teaches an embodiment of claim 21, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at –80oC).

With regard to claim 25, Lindpainter teaches an embodiment of claim 21, wherein the nucleic acid products consist of a first nucleic acid fragment of 123 base pairs, a second nucleic acid fragment of 157 base pairs and a third nucleic acid fragment of 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

With regard to claim 26, Lindpainter teaches an embodiment of claim 26, wherein:
a) when the first nucleic acid fragment is not present and the second and third nucleic acid fragments are present, the genotype is I/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype); and
b) when the first nucleic acid fragment is present and the second and the third nucleic acid fragments are not present, the genotype is D/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype).

With regard to claim 38 and 39, Lindpainter teaches an embodiment of claim 34, wherein the nucleic acid products consist of a first nucleic acid fragment of approximately 123 base pairs, a second nucleic acid fragment of 157 base pairs and a third nucleic acid fragment of 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

Lindpainter does not teach the limitation of claim 11, 19 or 33, c) wherein the first pair of flanking primers have the nucleic acid sequences SEQ ID NO: 1, SEQ ID NO:2 and the third primer has the nucleic acid sequence of SEQ ID NO:3.

Soubrier teaches the full-length sequence of intron 16 of the angiotensin converting enzyme and teaches the optimal location for primers for the amplification of the insertion region (Abstract, Figures 2A-B, col. 2, lines 9-50).

With regard to claim 11, Soubrier teaches an embodiment of claim 3, wherein the first pair of flanking primers have the nucleic acid sequence 5'-CCATCCTTTCTCCCATTTCTCT-3' (SEQ ID NO:1) and 5'-GGATGGTCTCGATCTCCTGA-3' (SEQ ID NO:2) and the third primer has the nucleic acid sequence 5'-CCTTAGCTCACCTCTGCTTGTAA-3' (SEQ ID NO:3) (see attached search report, where there is an exact match between nt 1416-1437 of SEQ ID 3 of Soubrier, which matches the 22 nt of SEQ ID NO:1).

With regard to claim 33, Soubrier teaches an embodiment of claim 30, wherein the pair of flanking primers have the nucleic acid sequences SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3 (see attached search report, where there is an exact match between nt 1416-1437 of SEQ ID 3 of Soubrier, which matches the 22 nt of SEQ ID NO:1).

Regarding claims 14-15 and 38-39, while Lindpainter does not disclose the specific amplicon sizes recited within the claim, it would have been obvious to one of ordinary skill in the art that if the primer locations were changed the amplicon size would change accordingly. Thus, an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and sequence length could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to adjust and optimize the location of the primers taught by Lindpainter, including those disclosed within the instant application and disclosed generally by Soubrier.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of angiotensin converting enzyme sequences, and concerning which a biochemist of ordinary skill would have attempted to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore, beyond the equivalence of primers taught by Buck and the obviousness of varying the locations within a given sequence, both Lindpainter and Soubrier give specific guidance with regards to the location of specific primer sequences and these are in line with the location of the primers disclosed in the instant application. For example, Lindpainter notes that they "used an optimized primer pair to amplify the D and I alleles" (p. 707, col. 2, 'determination of ace genotype' heading). Soubrier teaches that "the invention relates more particularly to pairs of distinct fragments selected from those previously mentioned, which can be used to design primers which can be used in sequence amplification procedures" (col. 2, lines 26-31). Furthermore, Soubrier teaches that "as a result of using two primers located on either side of at least a part of the polymorphic region, it is possible to easily visualize the difference in size due

to the presence of or absence of the insertion" (col. 4, lines 7-14). As Soubrier directly states a motivation to design primers within the sequence flanking the insertion in intron 16 of the ACE gene, it would have been obvious to combine the sequence disclosed by Soubrier with the additional step taught by Lindpainter of adding an additional primer(s) designed to hybridize directly within the insertion to arrive at the claimed invention with a reasonable expectation for success.

11. Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) as applies to claims 1, 3-10, 13, 34 and 36-37 and further in view of van Bockxmeer et al. (Circulation, 1995, vol. 92, p. 2066-71). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 1, 3-10, 13, 34 and 36-37 as recited in the 102 rejection stated above.

With regard to claim 29, Lindpainter teaches a method for identifying a patient with a heightened risk of suffering from a disease comprising:

a) determining the angiotensin converting enzyme (ACE) genotype in a sample from the patient by amplifying DNA from the sample with a first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 707, 'determination

of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples);

b) detecting three nucleic acid products of the amplification, wherein the nucleic acid products indicate the ACE genotype in the sample (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved);

With regard to claim 31, Lindpainter teaches an embodiment of claim 29, wherein the method distinguishes between genotypes selected from the group consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 1).

With regard to claim 32, Lindpainter teaches an embodiment of claim 29, wherein the genotype is determined by detecting the presence or absence of each of three nucleic acid products of the amplification reaction (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved).

Lindpainter does not teach the limitation of claim 29, recited as c) correlating the ACE genotype of the patient with a treatment regimen designed to treat or prevent one or more diseases selected from the group consisting of: myocardial infarction, ischemic and idiopathic dilated cardiomyopathy, sudden death in hypertrophic cardiomyopathy, coronary artherosclerosis, and restenosis after percutaneous transluminal coronary angioplasty.

With regard to claim 29, van Bockxmeer teaches a method which correlates the ACE genotype of the patient with a treatment regimen designed to treat or prevent one or more diseases selected from the group consisting of: myocardial infarction and restenosis after percutaneous transluminal coronary angioplasty (Table 1, where ACE genotype was correlated between angioplasty patients and control subjects, Table 2, where patient groups are

characterized in groups as either with or without restenosis, Table 3, where ACE genotypes were correlated with angioplasty patients with and without restenosis, Table 4, where ACE and ApoE genotypes were correlated with angioplasty patients with and without restenosis and Table 5, where changes in lesions were compared between patients with different ACE genotypes).

With regard to claim 30, van Bockxmeer teaches an embodiment of claim 29, wherein the treatment regimen is designed to treat myocardial infarction or coronary artherosclerosis (p. 3, 'subjects and protocol' heading, where the study was restricted to patients having elective percutaneous transluminal balloon coronary angioplasty (PTCA) of a previously untreated native coronary artery).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the genotyping technique taught by Lindpainter to the genotype association analysis taught by van Bockxmeer with a reasonable expectation for success. Both Lindpainter and van Bockxmeer are focused on studying the genotype of the angiotensin converting enzyme (ACE) and with the determination of any association between ACE genotype and treatment or risk of myocardial infarction. As noted by van Bockxmeer, "the ACE gene was postulated to be a candidate gene affecting the important clinical problem of restenosis after percutaneous transluminal balloon coronary angioplasty (PCTA) (Abstract). Given the obvious link between the studies conducted by Lindpainter and van Bockxmeer, it would have been obvious to substitute the genotyping method taught by Lindpainter to the method taught by van Bockxmeer with a reasonable expectation for success.

12. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) as applies to claims 1, 3-10, 13, 34 and 36-37 and further in view of Soubrier et al. (US Patent 6,736,323; April 1998) in view of Buck et al. (Biotechniques (1999) 27(3):528-536) and further in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 1, 3-10, 13, 34 and 36-37 as recited in the 102 rejection stated above. Lindpainter in view of Soubrier and Buck teach the limitations of claim 19. However, neither Lindpainter or Soubrier teach a step where the amplification comprises performing a single PCR amplification reaction.

With regard to claim 20, Lin teaches an embodiment of claim 19, wherein the amplification comprises performing a single polymerase chain reaction amplification (p. 662, col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the genotyping analysis of the ACE genotype, with three primers included in a PCR reaction simultaneously taught by Lin into the method of ACE genotyping with Lindpainter with a reasonable expectation for success. Both Lindpainter and Lin teach methods focused on the amplification of the 287 bp Alu insertion region within exon 16 of the ACE gene and both teach the inclusion of an insertion specific primer. The real-time PCR amplification technique taught by Lin "takes advantage of the SYBR Green I fluorescent dye for real-time detection of PCR product and, based on the length and nucleotide contents, for

the melting curve analysis of PCR products" (p. 661, col. 2 to p. 662, col. 1). Furthermore, the technique taught by Lin "provides a rapid and sensitive way for detection of ACE gene I/D polymorphism in clinical specimens" and "the applicability of real-time PCR to a high-throughput 96-well format should further reduce the overall time spent per sample and should be suitable for large-scale screening or research" (p. 665, col. 2). One of ordinary skill in the art would have recognized the benefit provided by the real-time PCR application taught by Lin and would therefore have been motivated to apply the technique to the method taught by Lindpainter with a reasonable expectation for success.

Relevant Prior Art

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Shanmugam et al. (PCR Methods and Applications, 1993, vol. 3, p. 120-121), Odawara et al. (Human Genetics, 1997, vol. 100, p. 163-166), Montgomery et al. (Circulation, 1997, vol. 96, p. 741-747), Frishberg et al. (Kidney International, 1998, vol. 54, p. 1843-2849), Pedersen-Bjergaard et al. (US PgPub 2003/0158090; August 2003) and Osterop et al. (Hypertension, 1998, vol. 32, p. 825-830) each disclose a variety of methods of amplification of the ACE insertion/deletion polymorphism within intron 16 using a third insertion-specific primer.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephanie K. Mummert

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JEFFREY FREDMAN
PRIMARY EXAMINER
3/17/06